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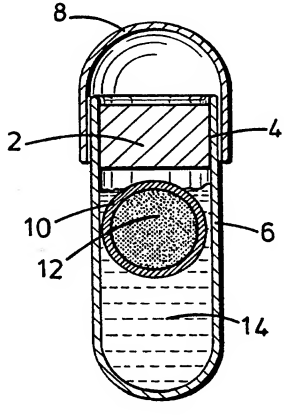
(54) Title: DEVICE FOR CONTROLLED DELIVERY OF LIQUIDS

(57) Abstract

A controlled release device for delivering a liquid substance to a patient at a predetermined time following administration comprises a male hydrogel plug (2) engaged in the neck (4) of a female body (6). The liquid substance (12) is contained within a container (10) formed of a water-soluble material retained within the device, thereby preventing interference or interaction of the liquid with the remainder of the device. When the device is placed in an aqueous environment (e.g., the gastrointestinal tract) the hydrogel plug swells and disengages after a predetermined time, exposing the water-soluble container to the aqueous environment, and dissolution thereof to release the liquid.



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DEVICE FOR CONTROLLED DELIVERY OF LIQUIDS.

TECHNICAL FIELD

The present invention relates to a controlled release device for delivering a liquid substance to a patient at a chosen time (e.g. 0.5 to 12 hours) following administration.

BACKGROUND

International patent specification WO90/09168 discloses a device of this type which comprises a water swellable male plug engaged within a female body. A pharmaceutically active material is contained within the device. When the device is exposed to water, the male hydrogel plug swells and eventually disengages itself from the female body, thereby allowing the pharmaceutically active material contained within the device to be released. It has been found that the time taken to release the pharmaceutical material is predictable and reproducible, so that the device may be used to release pharmaceutically active materials within the body of a patient after a predetermined time interval. This may be useful in the treatment of medical conditions where it is desirable to administer a pharmaceutically active material to the patient some time through the night, while the patient is asleep, so as to provide a desired level of the drug in the patient in accordance with his needs, for example

during the night or when he awakes. It may also be useful to allow dosing of materials at a predetermined point as the device passes through the gastro-intestinal tract, for example in the colon.

Whilst a device of this type is suitable for the administration of solid pharmaceutically active materials, the administration of liquids may pose problems. It may be desirable to administer active materials which are themselves liquids, or more commonly it may be useful to administer liquid formulations containing dissolved or dispersed active substances. Thus, where the active substance dissolves in water only slowly, it may be desirable to formulate this as a liquid formulation in order to facilitate absorption of the drug into the patient. For example, peptides may be formulated in liquid formulations.

The first problem with the inclusion of liquid formulations within the device, is the possibility that the liquid may interact with the materials used to form the wall of the female body. Whilst the body may be made from water insoluble materials, it may also be convenient to employ hard gelatin capsules which are coated on the outside with a water-insoluble coating but which may be dissolved by contact with aqueous formulations contained therein. Secondly, the time to disengagement of the plug depends upon the swelling characteristics of the hydrogel from which the plug is made. The presence of a liquid

formulation, particularly an aqueous formulation within the body is likely to detrimentally effect the plug disengagement time (i.e. the "pulse" time) or the reproducibility thereof. Finally, even if the liquid formulation does not interact with the materials of the device itself, there is a danger of liquid creeping between the plug and the inner surface of the neck of the device. This may lead to leakage of liquid. The lubricating action of the liquid is also likely to facilitate disengagement of the plug from the body which may again affect the pulse time.

Patent specification WO92/13521 (Alza Corporation) describes fluid-imbibing dispensing devices for delayed delivery of an active agent, which include an expansion means which absorbs fluid from a surrounding environment. The dispensing device comprises a housing having first and second wall sections telescopically engaged with each other, particularly a capsule having a hollow cap and a hollow body; either the cap or the body is in the form of a male section fitted inside the open end of the other female section. The expansion means is contained within the device and expands as it absorbs fluid, forcing apart the two sections of the device. The expansion means may be a swellable polymer or an osmotic formulation which swells as it absorbs fluid. In order to allow fluid to come into contact with the expansion means contained within the device, one of the wall sections adjacent to

the expansion means is fluid-permeable. After the sections are disengaged apart, fluid enters the device and comes into contact with the active agent contained within the device, thereby dispensing the active agent into the fluid.

It is an object of the present invention to address the problem of administering a liquid in a controlled release device.

SUMMARY OF THE INVENTION

The present invention provides a controlled release device for delivering a liquid substance, which comprises a male member engaged within a neck portion of a female body;
the device including a water-swellable material which swells so as to disengage the female body upon exposure of the device to an aqueous medium;
a container comprising a water-soluble material being retained within the device and containing the liquid substance to be delivered after disengagement of the male member and the female body.

The provision of the liquid within a container comprised of a water-soluble material, which is in turn located within the device provides a number of benefits. This arrangement isolates the liquid from the male member and the female body which form the controlled release device, and thus avoids any interaction of the liquid with

the materials thereof. Furthermore, any interference of the liquid with the controlled release device as described above which might affect the disengagement time of the male member and the female body is avoided.

A further benefit is that the container containing the liquid may itself be effectively expelled from the controlled release device into the surrounding aqueous environment e.g. within the gastro-intestinal tract. If the liquid is merely contained within the female body, it is found in practice that there are considerable difficulties in getting the liquid out of the body after the male plug disengages. These difficulties are exacerbated if the water content of the gastro-intestinal tract is low at the point of disengagement, or if the liquid is viscous or does not dissolve in water or mix easily therewith. Providing the liquid in a discrete container allows the container to be readily expelled from the device, when it may be more easily dissolved in the surrounding aqueous environment. This improves the reproducibility and speed of delivery of the liquid.

In a preferred embodiment, the male member is a plug formed of said water swellable material, such that as the plug swells it disengages from the female body. The plug is preferably formed of a water-swellable hydrogel, such as described in WO90/09168.

In another embodiment, the male member is a hollow member closed at one end, whose opposite open end engages

within the neck of the female body. A water swellable material is provided within the device which serves to disengage the female member after a predetermined time, by forcing the male member and the female body apart as the material swells in the presence of water. The swellable material inside the device may be an osmagent or an osmopolymer. Such an arrangement is disclosed in WO92/13521. In order to allow water to enter the device and to contact the water-swellable material a portion of the wall of the device adjacent thereto is preferably semipermeable; that is to say it is permeable to the passage of water into the device but impermeable to release of other substances from within the device.

The liquid substance may be any liquid but is particularly a pharmaceutically acceptable liquid which is to be administered to the patient, including liquids as such and liquid formulations. Liquid formulations may include one or more active agents dissolved, suspended, emulsified or admixed in a liquid carrier; and may include suitable formulation adjuncts such as suspending agents, emulsifiers, thickening agents and surfactants as will be apparent to the skilled man.

In one advantageous embodiment, the liquid formulation comprises a peptide or protein formulated in a liquid carrier, such as to provide a stable liquid environment for maintaining the activity of the peptide or protein and delivering it to the patient in a

pharmaceutically-effective manner.

Thus, the liquid substance is retained within the container until the male member has become disengaged and the contents of the device are subjected to the aqueous environment within the gastro-intestinal tract of the patient. Thereupon, the water-soluble container (or part thereof) dissolves rapidly (for example within 2 to 50 minutes) and releases the liquid substance.

The water-soluble material may be any suitable material known in the art and its characteristics will be chosen so as to be compatible with the liquid substance contained therein. For example, the container may be a hard gelatin container or a soft gelatin container. Other preferred materials include starch, agar, agarose, alginates, and water-soluble celluloses.

One or more water-soluble containers may be included within the device, depending on the volume of liquid substance to be delivered and other factors such as the rate of dissolution of the water-soluble material.

Generally, the container will be surrounded with a packing of an inert excipient, such as lactose, which does not impede the access of the aqueous gastrointestinal fluid to the water-soluble container. This prevents the container(s) from moving within the device during transport. In fact where the excipient is water soluble and/or contains a wetting agent, access of aqueous fluid into the capsule body may be assisted. Preferably, the

container is located close to the neck of the female body so as to readily be accessible to the gastro-intestinal fluid. The inert excipient may also contain a pharmaceutically active agent, particularly where such agent cannot be included in the liquid substance.

In order to assist expulsion of the liquid-containing container, an expandible excipient, such as a hydrogel powder, may be provided in the female body beneath the liquid container. When water enters the device the excipient expands and positively expels the liquid container, thereby improving the delivery of the liquid into the surrounding aqueous environment.

The liquid substance may be encapsulated within a container such as a capsule, having a discrete outer skin. Alternatively, the liquid may be contained within the pores of a porous water-soluble structure, particularly an open-cell foamed material.

Generally, the water-soluble container will be substantially spherical or ovoid and have a minimum width across its shortest dimension in the region 1 to 6mm.

Generally, the volume of liquid substance delivered will be in the range 1 to 300 microlitres.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

An embodiment of the present invention will now be described by way of example only in conjunction with the drawing wherein;

Figure 1 is a cross section to an enlarged scale of a controlled release device according to the present invention;

Figure 2 is a histogram showing the number of capsules which disengaged at a particular time, according to Example 2;

Figure 3 is a histogram showing the results of Example 3; and

Figure 4 is a drug release profile showing the results of Example 4.

The device comprises a male plug 2 formed of a hydrogel material inserted in neck 4 of female body 6. The device is closed with a cap 8 of water-soluble material.

Within the body 6 is a container in the form of a soft gelatin capsule 10 containing a liquid formulation 12. Alternatively, the capsule could be a hard gelatin capsule formed in two interengaging hollow sections and sealed to prevent egress of liquid. The capsule is surrounded by a packing 14 of an inert excipient, such as lactose. This helps locate the capsule and prevents movement during transport. Alternatively the container may be placed on a bed of a swellable material in order to assist ejection thereof from the capsule body.

The male plug 2 is formed of a hydrogel material (such as disclosed in W090/09168) and is usually inserted so that the upper end of the plug is level with or below

the upper end of the neck 4.

The cap 8 is formed of a water-soluble material, such as gelatin, which dissolves quickly in the stomach after administration to the patient. The body 6 is formed of a water-insoluble material, which may be a water-insoluble plastics material or may be gelatin coated with a water-impermeable coating (such as disclosed in WO90/09168).

When the device is administered to a patient, the aqueous environment in the gastro-intestinal tract quickly dissolves the water-soluble cap. Water is then absorbed into the hydrogel plug 2, which swells and is expelled from the body 6 after a predetermined time interval (for example 2 to 10 hours). This allows the contents of the device to be released into the patient's gastro-intestinal tract. Once the water-soluble capsule 10 comes into contact with the aqueous fluid from the gastro-intestinal tract, the water-soluble material quickly dissolves and liberates the liquid formulation into the patient's gastro-intestinal tract. In order to allow good control of the drug release time, the time for dissolution of the water-soluble capsule and release of the liquid formulation is short (e.g. 2 to 20 minutes) compared to the disengagement time of the plug. After disengagement, the capsule may dissolve in situ - liquid being released therefrom as soon as a portion of the capsule wall dissolves away; or the capsule may come out of the device

into the gastro-intestinal tract and become dissolved there.

EXAMPLE 1 (Hydrogel production)

Hydrogel rods were prepared by polymerising 6,000 grams of polyethylene glycol PEG 8000 (Pharma) of number molecular weight Mn 8700 and ratio Mw/Mn = 1.03 (where Mw is the mean molecular weight) with 111.04 grams of hexanetriol, 506.8 grams of Desmodur W (dicyclohexylmethane-4,4-diisocyanate), and catalysed by 0.6 grams of anhydrous ferric chloride. The mole ratios were PEG 8000 (1 mole), hexanetriol (1.2 moles), Desmodur W (2.8 moles) and ferric chloride (0.01% by weight of PEG). The PEG 8000 was melted and dried to less than 0.05% w/w moisture content in a Buchi Rotavapor at 95°C, at a pressure less than 5 millibars for a period of two hours. Then, the ferric chloride was dissolved in the hexanetriol at 75°C, and the mixture stirred into the dried PEG for 5 minutes at 100 rpm. The mixture at 85°C was then mixed with the Desmodur W by pumping into a mixer rotating at 1500 revolutions per minute. Molten polymer at about 80°C was then dispensed into tubular polytetrafluoroethylene moulds 35cm long under a vacuum of less than 50 millibars. Curing took place at 95°C for 4 hours in a fan equipped oven. The polymer rods were then allowed to cool.

The hydrogel rods are washed by immersion in a circulating stream of water containing butylated hydroxy

anisole (BHA) as a stabiliser.

The washing removed water-soluble extractable substance from the polymer and the BHA stabiliser becomes incorporated into the polymer.

The swelling factor is defined as (Ws-Wd)/Wd x 100, where Ws is the swollen weight and Wd is the dry weight. The hydrogels were found to have a swelling factor of 270± 25.

The hydrogel rod was then cut into plugs, each generally of a nominal length 4mm.

EXAMPLE 2 (Release of liquid)

Tests to determine plug ejection times were carried out on a batch of 24 devices of the type shown in Figure 1. Each device contained a soft gelatin capsule container size 1 round (approximate volume 60 microlitres and approximate diameter 2mm) filled with an oily liquid. The capsule was placed on a bed of a packed powdered hydrogel (of the type produced in Example 1) within the capsule body. The devices were placed into a water bath at 37°C stirred by a stirrer at 50 rpm. The time taken for each plug to disengage from the female body was observed visual and the results are shown in Figure 2.

Figure 2 shows the number of the devices which disengaged at each particular time. The mean time to disengagement was 4.92 hrs (standard deviation 0.23) and all devices disengaged within the range 4.50 to 5.25 hrs.

After disengagement it was visually observed that in every case the soft gelatin liquid container was rapidly ejected from the device body due to swelling and expansion of the hydrogel powder which pushed the soft gelatin container out of the body; the time taken being from 0 to 1 minutes.

Therefter the liquid fill was released from the soft gelatin container as the container dissolved in the surrounding water, in a time range of about 1 to 5 minutes.

EXAMPLE 3 (Release of liquid)

A further 24 devices were tested following the procedure outlined in Example 2.

In this case the soft gelatin container was placed on a packed bed comprising a mixture of 99.5 wt% sucrose powder and 0.5 wt% sodium docusate.

Figure 3 shows the plug disengagement times for the devices. The mean time to disengagement was 4.77 hrs (standard deviation 0.13) and all devices disengaged in the time range 4.50 to 5.00 hrs.

In this case the soft gelatin containers were not ejected from the device bodies. However, the sucrose-sodium docusate fill encouraged the ingress of water into the capsule body after disengagement of the plug. The liquid was observed to be released from the soft gelatin containers within 2 to 3 minutes after disengagement.

EXAMPLE 4 (Release of Liquid Drug Formulation)

Six devices were tested following the procedure outlined in Example 2. Each device included a soft gelatin capsule container (size 1 round) which contained a model drug (metoclopramide) in a polyethylene glycol (PEG400) liquid vehicle. The soft gelatin container was placed on a bed of packed hydrogel (of the type produced in Example 1) powder.

The release of metoclopramide into the surrounding water was monitored by UV spectroscopy and the results for the 6 capsules are shown in Figure 4. It can be seen that all capsules released the drug at a well defined time.

It was observed that all the soft gelatin containers were ejected from the device body due to the swelling of the hydrogel powder, in a time range of 1 to 10 minutes following disengagement of the plug. Thereafter the liquid fill was released from the soft gelatin containers by dissolution thereof in a time range of 2 to 10 minutes.

CLAIMS

1. A controlled release device for delivering a liquid substance, which comprises a male member (2) engaged within a neck portion (4) of a female body (6);
the device including a water-swellable material which swells so as to disengage the female body upon exposure of the device to an aqueous medium;
a container (10) comprising a water-soluble material being retained within the device and containing the liquid substance (12) to be delivered after disengagement of the male member and the female body.

2. A device according to claim 1 wherein the male member is a plug formed of said water-swellable material.

3. A device according to any preceding claim wherein the water-swellable material is a hydrogel.

4. A device according to any preceding claim wherein the container is a capsule formed of a water-soluble material.

5. A device according to claim 4 wherein the container is a hard gelatin or a soft gelatin capsule.

6. A device according to any preceding claim which further comprises an inert excipient (14) within the device, the container being located on or within the excipient.

7. A device according to any preceding claim wherein the container is substantially spherical or ovoid and has a minimum width across its shortest dimension in the region 1 to 6mm.

8. A device according to any preceding claim wherein the volume of liquid substance contained within the device is in the range 1 to 300 microlitres.

9. A device according to any preceding claim wherein the liquid substance is released from the container within 2 to 20 minutes after disengagement of the male member and female body.

10. A device according to any preceding claim wherein the liquid substance is incompatible with material forming the male member or the female body.

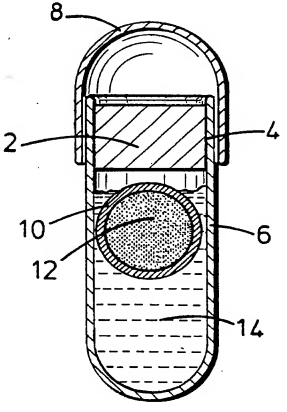
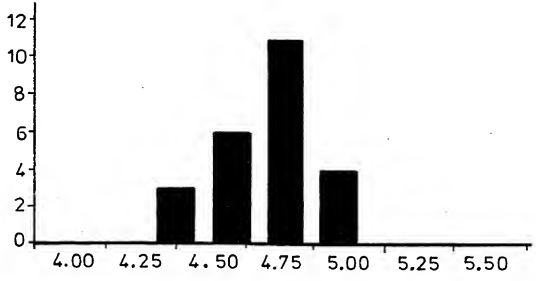


FIG. 1


12
10
8
6
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4.75
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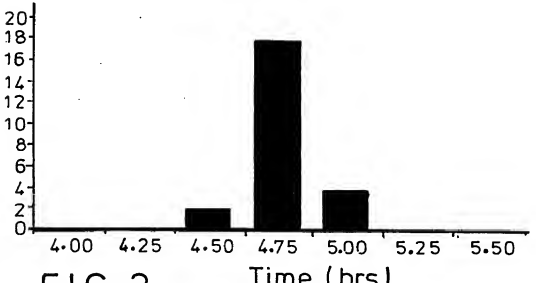
5.25
5.50
Time (hrs)

FIG. 2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5.25
5.50
Time (hrs)

FIG. 3

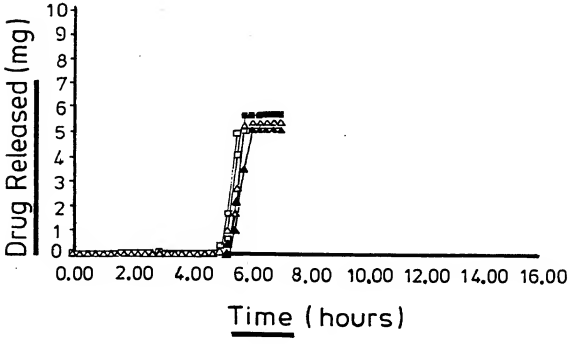
Drug Released (mg)
10
9
8
7
6
5
4
3
2
1
0
0.00 2.00 4.00 6.00 8.00 10.00 12.00 14.00 16.00
Time (hours)

FIG. 4

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/GB 94/02205

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO,A,91 12795 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 5 September 1991 see the whole document ---	1-4,7-10
X	EP,A,0 384 642 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 29 August 1990 see the whole document -----	1-4,7-10

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Information on patent family members

Internat. Application No PCT/GB 94/02205

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